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Regulatory Updates and a Perspective on Biologics in Japan

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Pharmaceuticals and Medical Devices Agency (PMDA), Japan

The views expressed in this presentation are those of the author and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency.

Agenda

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■Regulatory Updates in Japan

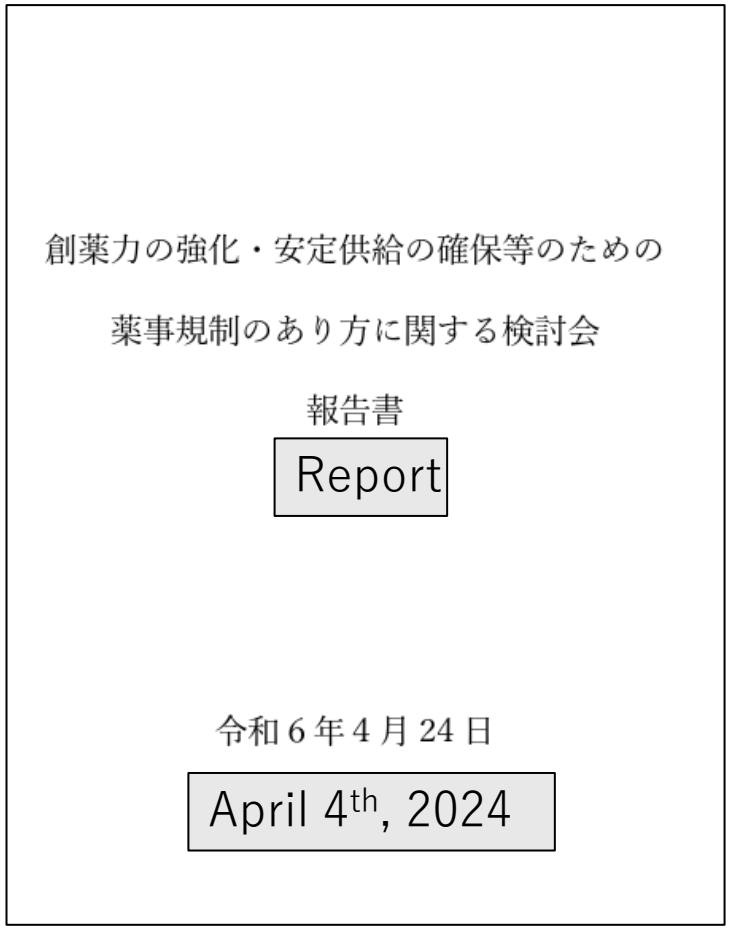
1. Post-approval Change for Moderate risk (trial)

2. Publications

3. Scientific Guidelines

Review Committee on Pharmaceutical Regulation for Strengthening Drug Discovery Capabilities and Securing Stable Supply

- Summary of considerations
  - Promotion of pharmaceutical development
  - Clinical trials
  - Post-marketing safety measures
  - Dissemination of information
  - Quality


創薬力の強化・安定供給の確保等のための

薬事規制のあり方に関する検討会

報告書

Report

令和６年４月24日

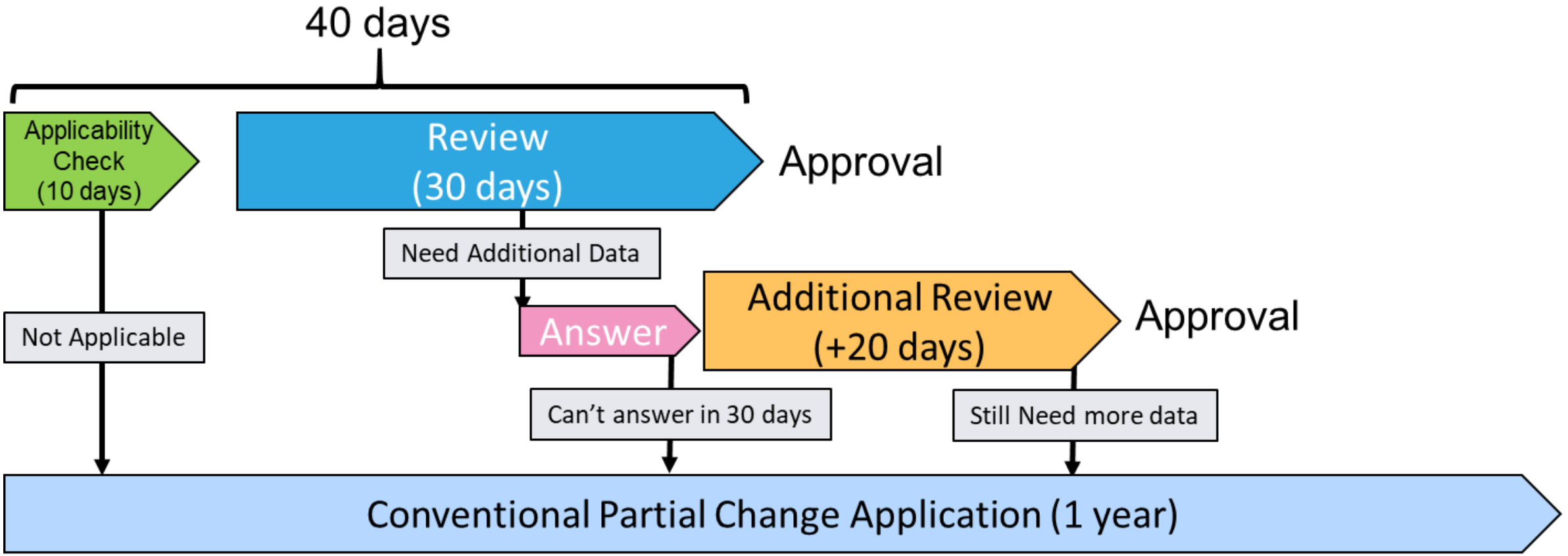
April 4th, 2024

https://www.mhlw.go.jp/content/11121000/001248959.pdf

Post-Approval Change Reporting Categories

ICH Q12 Classification	Japan	US	EU
Prior Approval	PCA (Partial Change Application)	PAS (Prior Approval Supplement)	Type II Variation
Notification Moderate	**Trial Start!!**	CBE-30	Type IB Variation
Notification Low	MCN (Minor Change Notification) **Trial Start!!** Not Approved Matters	CBE-0 Annual Report	Type IA_{IN} Variation Type IA Variation
Not Reported			

Partial Change Application 40 (Trial version)



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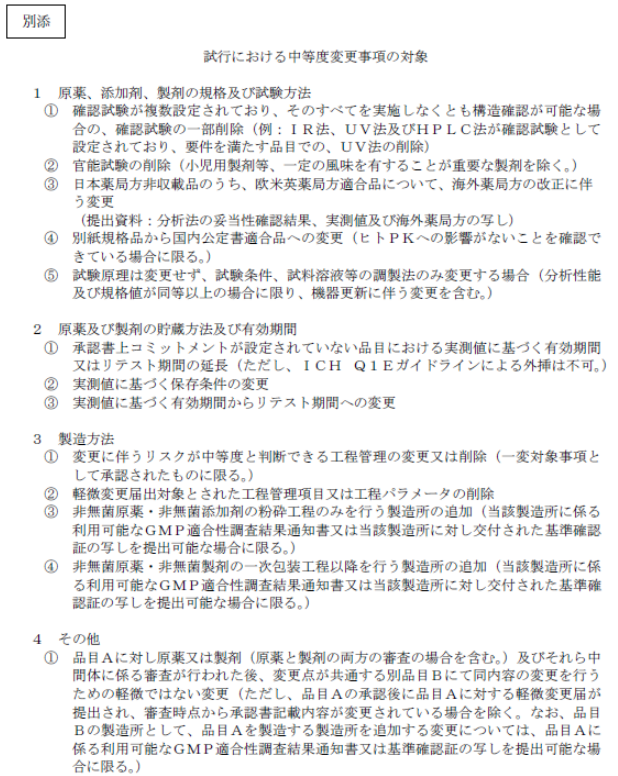
Criteria of Partial Change Application 40 (Trial version)

The Criteria of PCA-40 is based on EP Guideline.

Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52013XC0802(04)&from=EN



別添

試行における中等度変更事項の対象

1　原薬、添加剤、製剤の規格及び試験方法
① 確認試験が複数設定されており、そのすべてを実施しなくとも構造確認が可能な場合の、確認試験の一部削除（例：ＩＲ法、ＵＶ法及びＨＰＬＣ法が確認試験として設定されており、要件を満たす品目での、ＵＶ法の削除）
② 官能試験の削除（小児用製剤等、一定の風味を有することが重要な製剤を除く。）
③ 日本薬局方非収載品のうち、欧米英薬局方適合品について、海外薬局方の改正に伴う変更
（提出資料：分析法の妥当性確認結果、実測値及び海外薬局方の写し）
④ 別紙規格品から国内公定書適合品への変更（ヒトＰＫへの影響がないことを確認できている場合に限る。）
⑤ 試験原理は変更せず、試験条件、試料溶液等の調製法のみ変更する場合（分析性能及び規格値が同等以上の場合に限り、機器更新に伴う変更を含む。）

2　原薬及び製剤の貯蔵方法及び有効期間
① 承認書上コミットメントが設定されていない品目における実測値に基づく有効期間又はリテスト期間の延長（ただし、ＩＣＨ　Ｑ１Ｅガイドラインによる外挿は不可。）
② 実測値に基づく保存条件の変更
③ 実測値に基づく有効期間からリテスト期間への変更

3　製造方法
① 変更に伴うリスクが中等度と判断できる工程管理の変更又は削除（一変対象事項として承認されたものに限る。）
② 軽微変更届出対象とされた工程管理項目又は工程パラメータの削除
③ 非無菌原薬・非無菌添加剤の粉砕工程のみを行う製造所の追加（当該製造所に係る利用可能なＧＭＰ適合性調査結果通知書又は当該製造所に対し交付された基準確認証の写しを提出可能な場合に限る。）
④ 非無菌原薬・非無菌製剤の一次包装工程以降を行う製造所の追加（当該製造所に係る利用可能なＧＭＰ適合性調査結果通知書又は当該製造所に対し交付された基準確認証の写しを提出可能な場合に限る。）

4　その他
① 品目Ａに対し原薬又は製剤（原薬と製剤の両方の審査の場合を含む。）及びそれら中間体に係る審査が行われた後、変更点が共通する別品目Ｂにて同内容の変更を行うための軽微ではない変更（ただし、品目Ａの承認後に品目Ａに対する軽微変更届が提出され、審査時点から承認書記載内容が変更されている場合を除く。なお、品目Ｂの製造所として、品目Ａを製造する製造所を追加する変更については、品目Ａに係る利用可能なＧＭＰ適合性調査結果通知書又は基準確認証の写しを提出可能な場合に限る。）

In general, these criteria are mainly for chemical products.

For biologics (Examples)

- Change in storage conditions for biologics, when the stability studies have not been performed in accordance with an approved stability protocol.
- Change in parameter for manufacturing process, when the impact against quality is clarified as moderate.

Vague. Need Consultation!

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Agenda

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1. Post-approval Change for Moderate risk (trial)

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PMDA Fifth Mid-term Plan (FY2024-FY2028)

Improving operational quality through the promotion of RS	
Strengthening human resources	• Develop personnel with an understanding of clinical and related settings through exchanges with external institutions, including those with Comprehensive Partnership Agreements • Develop professionals capable of leading scientific discussions through active engagement in RS activities
Enhancing scientific evidence	• Strengthen organizational research capacity by expanding research efforts • Establish a system for consolidating issues on the review and consultation to facilitate cross-departmental discussion
Strengthening public communications	• Publish findings from RS research and related activities in English-language journals and other academic platforms
Contributing to the further utilization of medical information	• Further improve the accessibility of the Medical Information Database Network(MID-NET®) • Disseminate information on the standardization and quality control of medical information

Enhancing scientific evidence: Science Board and Early Consideration

Strengthening public communications: Regulatory Science Research

https://www.pmda.go.jp/files/000277557.pdf

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PMDA Regulatory Science Research

Expanding the biologics in new drug approvals in Japan

Two-thirds of the new drugs approved in Japan in FY2023 are biological drugs

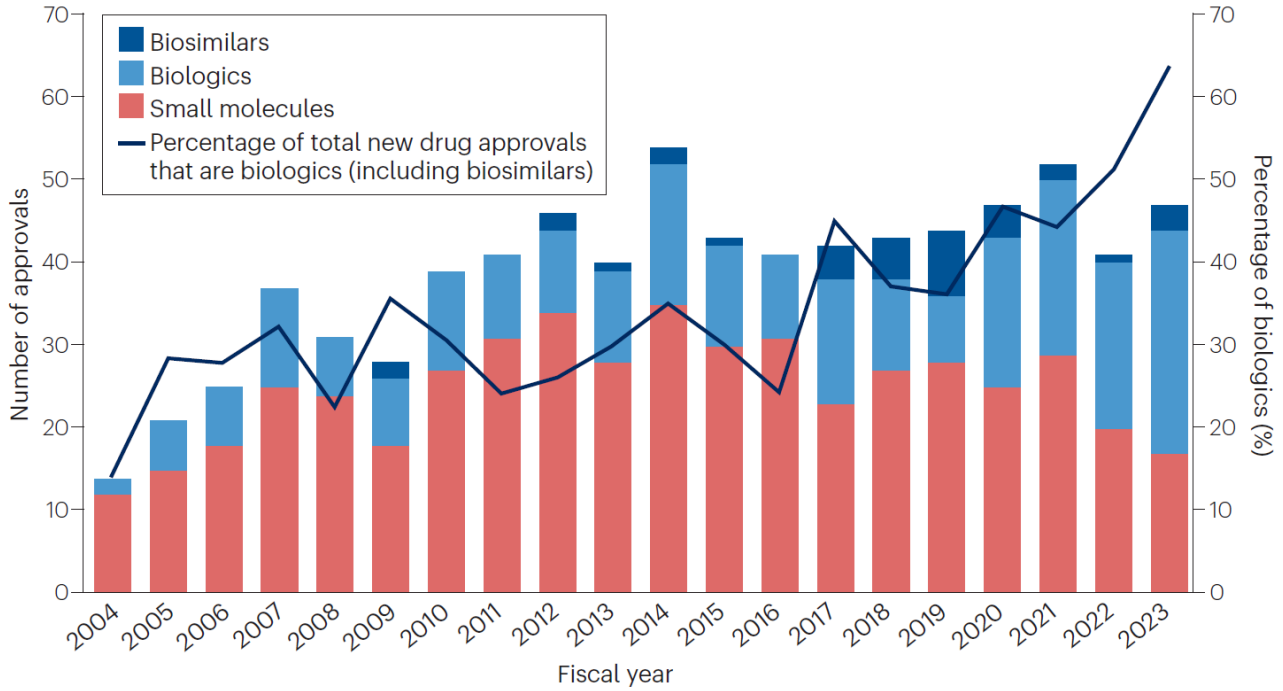
nature reviews drug discovery

FROM THE ANALYST'S COUCH | 02 October 2024 | Correction 28 October 2024

Two decades of new drug approvals in Japan

By Ryosuke Kuribayashi, Aya Hariu, Yasuhiro Kishioka & Akira Sakurai

The Pharmaceuticals and Medical Devices Agency (PMDA) was established in fiscal year (FY) 2004 to evaluate the quality, efficacy and safety of drugs and medical devices for marketing authorization in Japan. Here, we analyse trends in the new drugs reviewed and approved by the PMDA and Ministry of Health, Labour and Welfare (MHLW) in the 20 years from FY2004.



Kuribayashi R. et al. Nature Reviews Drug Discovery. 24, 12-13 (2025)

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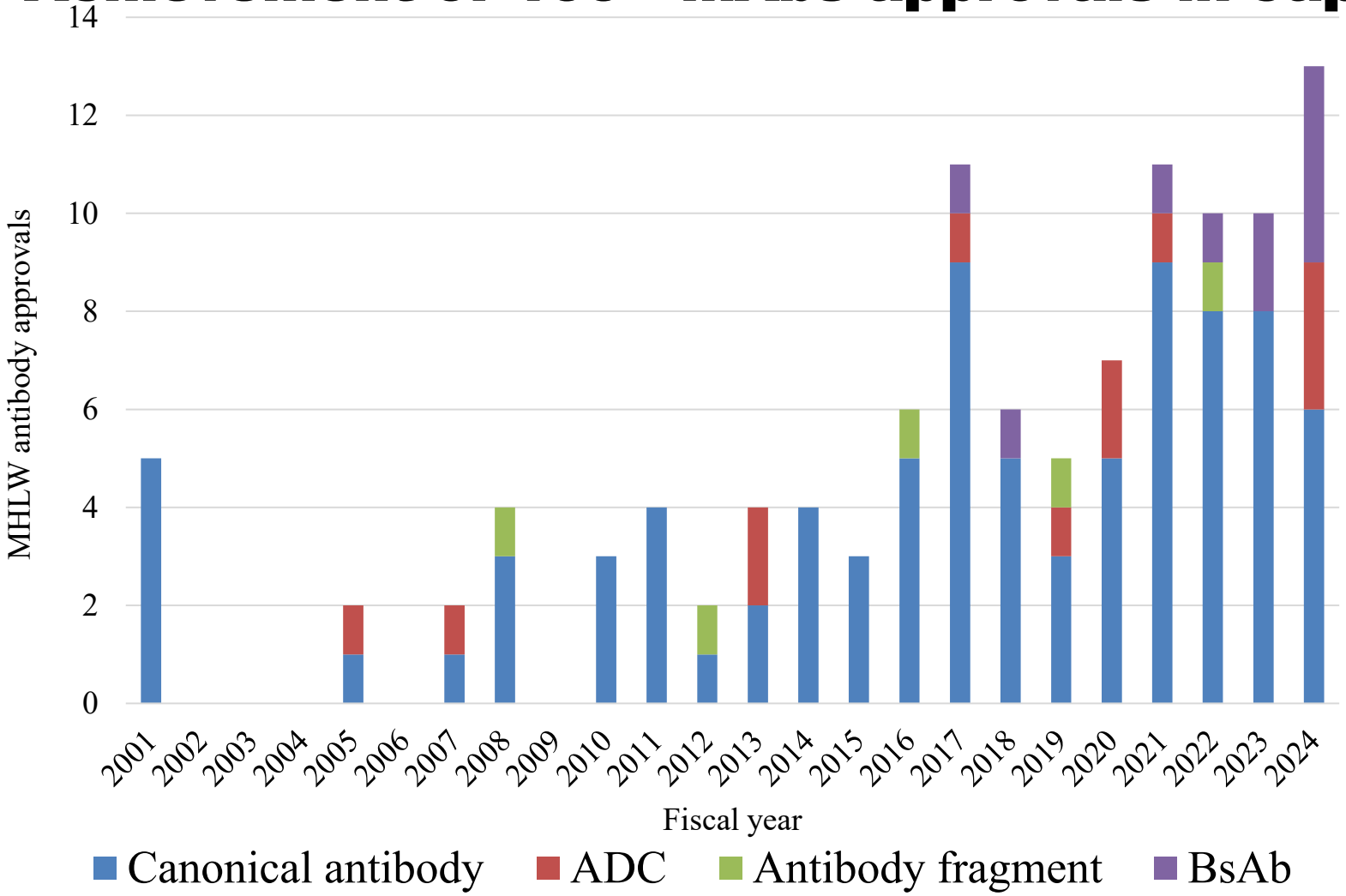
PMDA Regulatory Science Research

Achievement of 100th mAbs approvals in Japan



- ADCs and bi-specifics have been emerging as important contributors to overall approvals.
- The approval of large number of ADCs and bi-specifics will be expected in Japan.

Adapted from Hariu A, et al. AAPS J. 27: 105 (2025)

ICH M18

In ICH Assembly meeting, Madrid, May 2025, the new topic for harmonization was adopted.

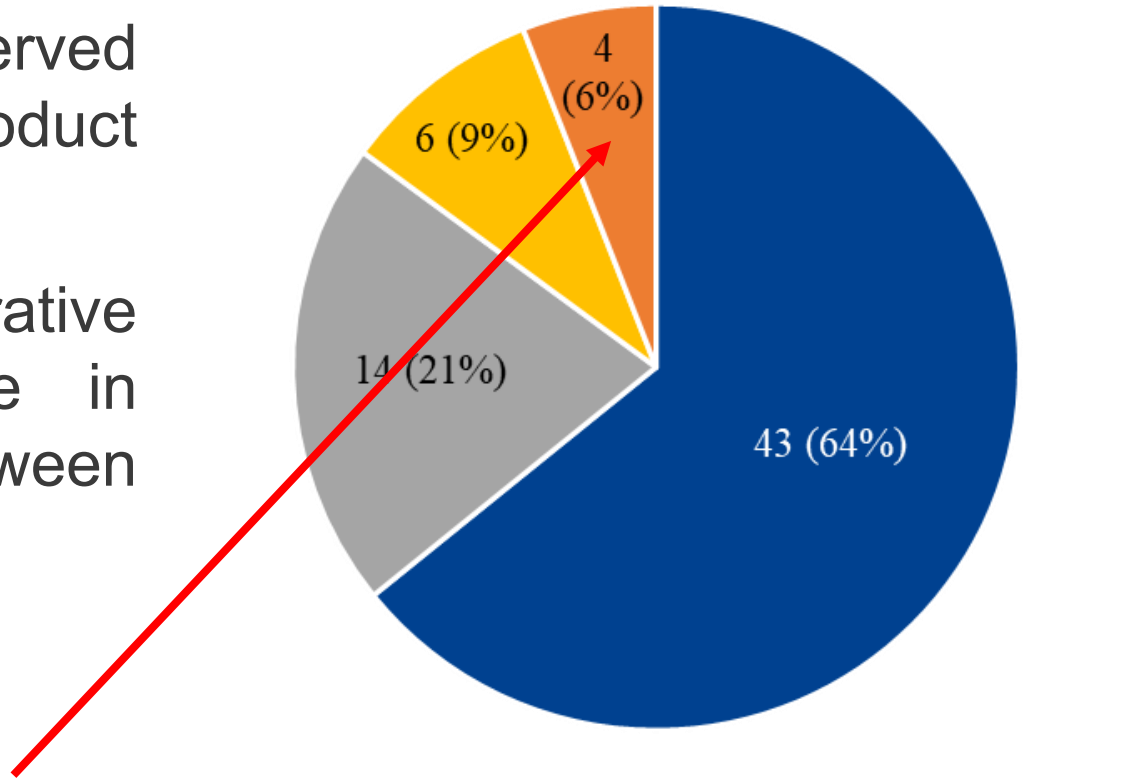
“Framework for Determining Utility of Comparative Efficacy Studies in Biosimilar Development Programs”

– a new ICH Multidisciplinary Guideline to address factors to consider in determining the utility of comparative efficacy studies in biosimilar development programs

https://ich.org/pressrelease/press-release-ich-assembly-meeting-madrid-spain-may-2025

PMDA Regulatory Science Research

- We investigated which studies justified the differences in quality attributes observed between biosimilar and its reference product in the 18 antibody drugs.
- These findings indicate that comparative efficacy studies play a limited role in establishing comparability between biosimilars and their RPs.



Only 6% of QA differences were justified through findings from comparative efficacy studies.

Goto K. et al. Pharmaceut Med. 39(6), 477-491 (2025) https://doi.org.10.1007/s40290-025-00583-w

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PMDA Regulatory Science Research

Biosimilar void: defined as a situation in which biosimilars are not yet developed globally within reference products approved in Japan between FY 2004 and 2016

Nonproprietary name	Type	Orphan
Follitropin beta	Hormone	
Gemtuzumab ozogamicin	mAb	O
Agalsidase alfa	Enzyme	O
Pegvisomant	Hormone	O
Alglucosidase alfa	Enzyme	O
Idursulfase	Enzyme	O
Insulin detemir	Hormone	
Ibritumomab tiuxetan	mAb	O
Galsulfase	Enzyme	O
Thyrotropin human alfa	Hormone	O
Insulin glulisine	Hormone	
Rasburicase	Enzyme	
Panitumumab	mAb	
Epoetin beta pegol	ESA	
Dornase alfa	Enzyme	O

Nonproprietary name	Type	Orphan
Mogamulizumab	mAb	O
Insulin degludec	Hormone	
Certolizumab pegol	mAb	
Metreleptin	Hormone	O
Brentuximab vedotin	mAb	O
Velaglucerase alfa	Enzyme	O
Alemtuzumab	mAb	O
Elosulfase alfa	Enzyme	O
Dulaglutide	Hormone	
Asfotase alfa	Enzyme	O
Evolocumab	mAb	
Ixekizumab	mAb	
Brodalumab	mAb	
Choriogonadotropin alfa	Hormone	

- 29 candidates of biosimilar void
- 16 candidates being orphan drugs

Adapted from Hariu A, et al. Naunyn-Schmiedeberg's Archives of Pharmacology. 2025. https://doi.org/10.1007/s00210-025-04494-0

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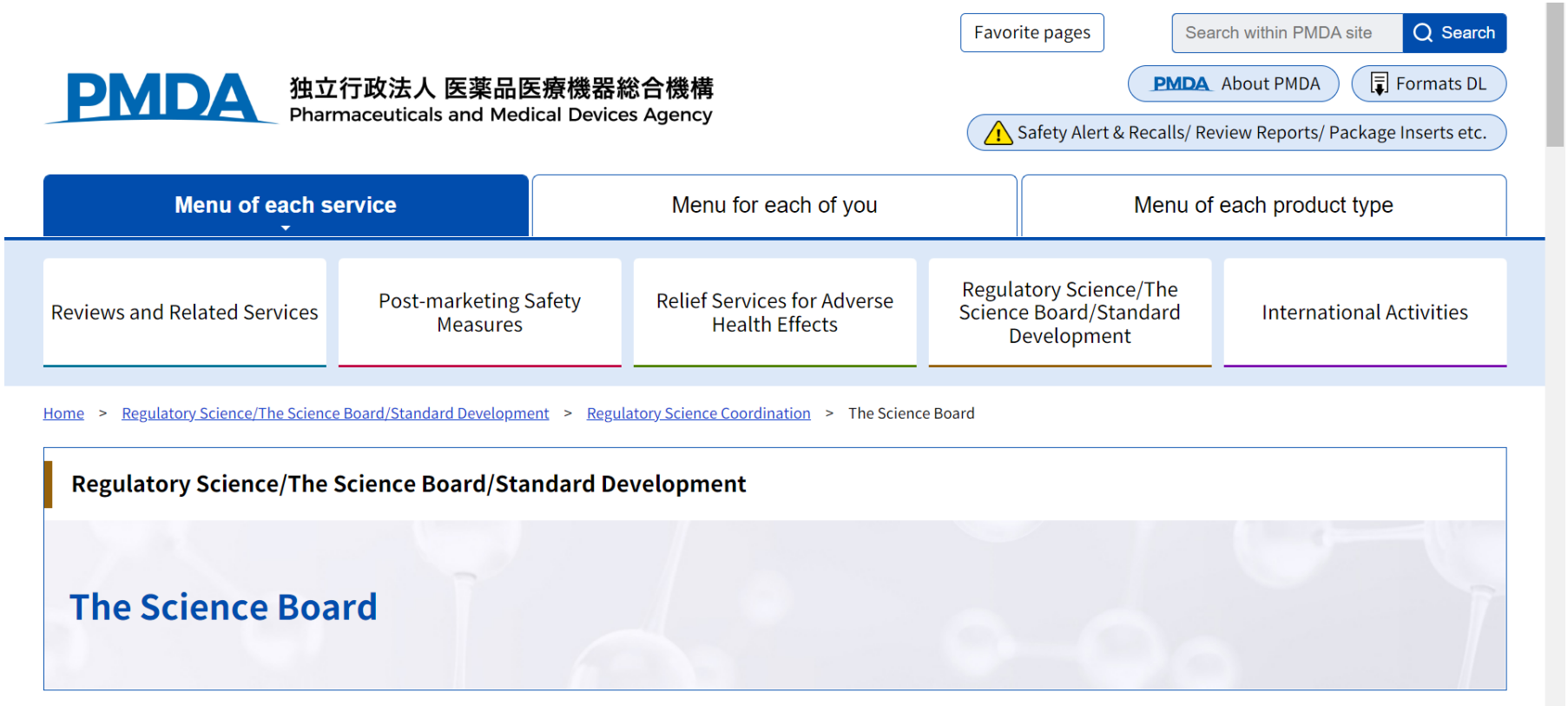
The Science Board, PMDA

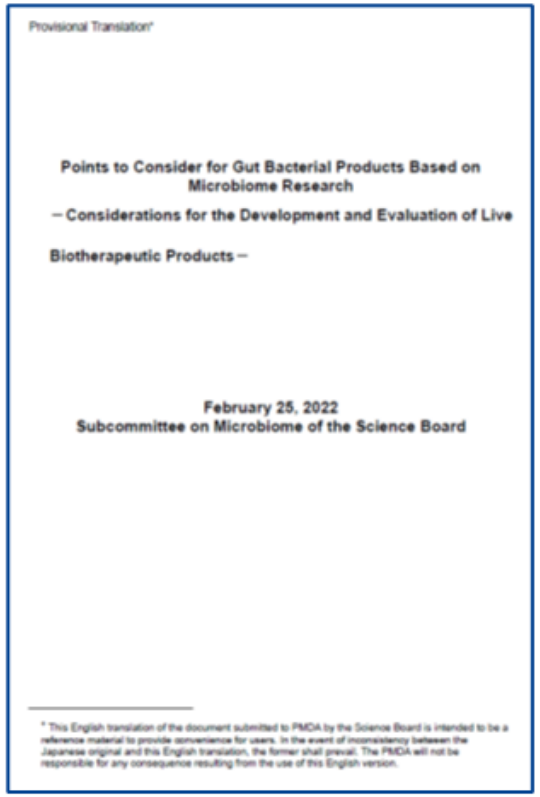
The purposes of the Science Board are, advancing regulatory science and evaluate products with advanced science and technology in appropriate manner by enhancing cooperation and communication with academia and medical institutions, based on PMDA's philosophy to deliver safe and effective drugs, medical devices and regenerative medical products to the people and further promotion of medical innovations.



https://www.pmda.go.jp/english/rs-sb-std/sb/science-committee/0010.html

Microbiome medicines for LBPs

- Report from PMDA Science Board (25 Feb, 2022)



Provisional Translation*

Points to Consider for Gut Bacterial Products Based on Microbiome Research

– Considerations for the Development and Evaluation of Live Biotherapeutic Products –

February 25, 2022
Subcommittee on Microbiome of the Science Board

* This English translation of the document submitted to PMDA by the Science Board is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.

Table of Content

https://www.pmda.go.jp/files/000249812.pdf (in English)

FMT; Fecal Microbiota Transplantation
LBPs; Live Biotherapeutic Products

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Microbiome medicines for LBPs

Quality Aspects for LBP

✓ In silico safety evaluation

Toxin-related genes, Antibiotic resistance genes, Mobile genes such as transposons

✓ Analyze and Characterization of MCB/WCB

Genotype and Phenotype

Characteristic Items		Considerations for conducting the test
Genotype	16S rRNA gene sequence	16S rRNA gene sequence unique to the strain: purity and identity of the target strain
	Whole Nucleotide Sequence Analysis	
Phenotype	Protein Expression Profiles	MALDI-TOF MS analysis: purity and identity of target strains (may vary depending on culture conditions)
	Morphology	Observation under the microscope, colony morphology
	Gram stainability	
	Ability to produce useful substances	Indicators related to drug efficacy and biological activity
	Proliferative properties	Depends on culture conditions
	Drug resistance	
Purity test		Heterologous microorganism denial test

https://www.pmda.go.jp/files/000249812.pdf

Extracellular Vesicles (EVs)

- Report from PMDA Science Board (17 Jan, 2023)


エクソソームを含む細胞外小胞(EV)を利用した治療用製剤に関する報告書

目次

Table of Content

https://www.pmda.go.jp/files/000268368.pdf (in English)

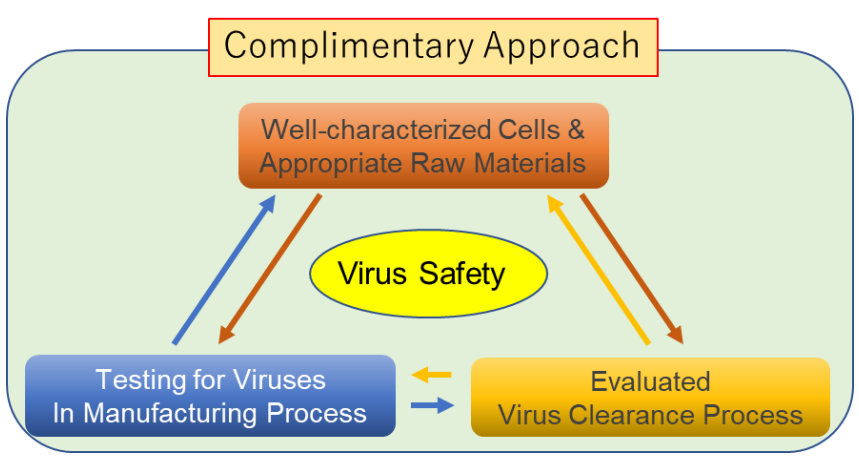
Extracellular Vesicles (EVs)

Virus safety related process
Conventional Biologics VS EV products

	Conventional Biologics	EV products
Cells	Well-characterized Cell line	Not Well-characterized MSC, primary cell, etc.
Nanofiltration（15～35nm）	Effective	Remove both EVs and viruses
Low-pH, Detergents, S/D treatment	Effective	Inactivate both EVs and viruses
Affinity Columns	Effective	Buffers will affect EVs
Other purification	Effective	Developing
Concentration Diafiltration	Remove only virus	Concentrate both EVs and viruses

Extracellular Vesicles (EVs)

Concept of virus safety for EV products



General concept

- ✓ Virus safety may be assured by two principles of Well-characterized Cells and Appropriate raw materials and Testing for Viruses in Manufacturing process.
- ✓ The PMDA highly recommends to have a discussion about the virus safety from the early stage as soon as possible with the developers.

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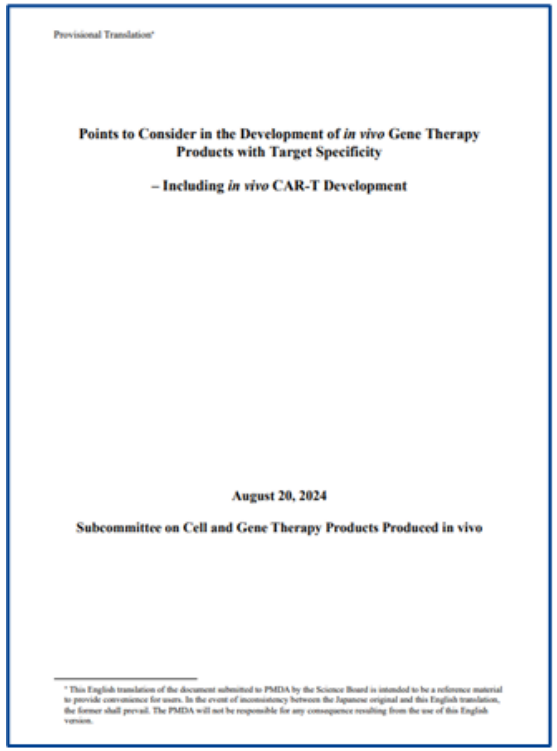
In vivo Gene Therapy Products with Target Specificity

- Report from PMDA Science Board (20 August, 2024)



Provisional Translation*

Points to Consider in the Development of *in vivo* Gene Therapy Products with Target Specificity

– Including *in vivo* CAR-T Development

August 20, 2024

Subcommittee on Cell and Gene Therapy Products Produced in vivo

* This English translation of the document submitted to PMDA by the Science Board is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.

Table of Content

https://www.pmda.go.jp/files/000270120.pdf (in English)

Early Consideration

- ***Early Consideration is reference information and point of view at that time*** *for promoting the practical application of new technologies and other innovations and the development of innovative pharmaceuticals, etc.,* ***although scientific knowledge and information have not yet been fully accumulated****.*

Recent Early Consideration

- ☐ Points to consider for externally controlled trials
- ☐ Points to consider for nonclinical safety matters when submitting the initial clinical trial notification
- ☐ Points to consider for the discussion with PMDA using the ICH S1B (R1) guideline and in the approval application
- ☐ Points to consider in developing drugs for pediatric inflammatory bowel disease
- ☐ Points to Consider for Clinical Efficacy Evaluation of Drugs for Palmoplantar Pustulosis

https://www.pmda.go.jp/english/review-services/regulatory-info/0005.html

Quality of Fecal Microbiota Transplantation (FMT) (Early Consideration)

FMT is a treatment in which intestinal bacteria prepared from stool derived from a healthy donor are transplanted into the patient.

PMDA have published the Early Consideration on **Quality of FMT for Early developments (focused on safety)** in Nov 2025.

- ✓ Donor screening
- ✓ Quality control

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https://www.pmda.go.jp/files/000278117.pdf (in English)

Quality of Fecal Microbiota Transplantation (FMT) (Early Consideration)

Donor screening (feces and Blood screening)

Table 1 Test items for pathogens to be ruled out

Test item	
Donor feces	
Bacteria/fungi	
Aeromonas	*Campylobacter*
Toxigenic *Clostridium difficile*	Enteroinvasive *Escherichia coli*
Enteroaggregative *Escherichia coli*	Enterotoxigenic *Escherichia coli*
Enteropathogenic *Escherichia coli*	Enterohemorrhagic *Escherichia coli* (Shiga toxin-producing *Escherichia coli*)
Shigella	*Salmonella*
Vibrio	*Vibrio cholerae*
Yersinia enterocolitica	*Plesiomonas shigelloides*
Listeria monocytogenes	*Helicobacter pylori*
Toxigenic *Staphylococcus aureus*	Vancomycin-resistant *enterococci*

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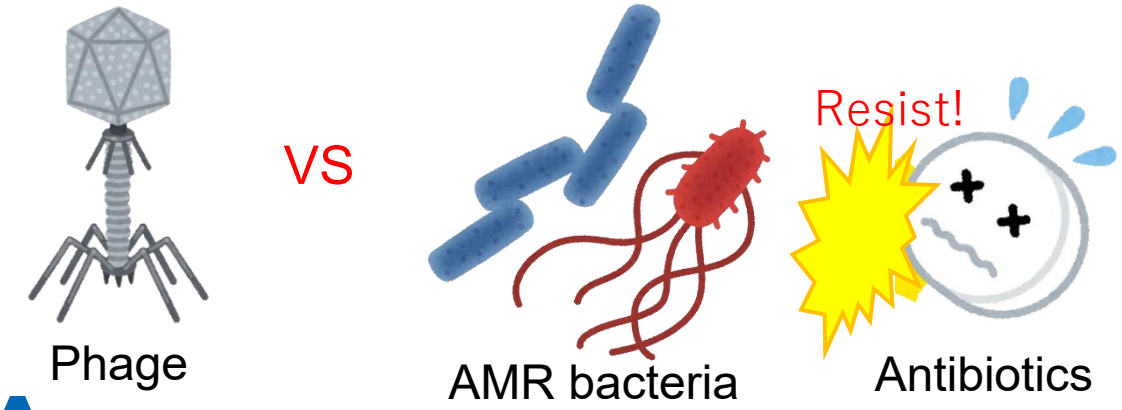
https://www.pmda.go.jp/files/000278117.pdf (in English)

Upcoming Guideline (The Science Board)

Considerations for Developing Phage Therapy Medicinal Products for the Treatment of Antimicrobial Resistant Bacterial

- ✓ Latest information and approach to development of Phage Therapy Medicinal Products (PTMP)
- ✓ Precautions for quality, non-clinical, and pharmacology before clinical trials
- ✓ Precautions to facilitate development, such as the concept of risk foreseeable in the clinical use of PTMP

https://www.pmda.go.jp/files/000274716.pdf



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Upcoming Guideline

FY2021 Establishment of “Subcommittee on Therapeutic Products Based on Extracellular Vesicles (EVs) Including Exosomes” in PMDA

FY2023 Publication https://www.pmda.go.jp/files/000268368.pdf
①Report on Therapeutic Products Based on Extracellular Vesicles (EVs) Including Exosomes

FY2024 Publication https://link.springer.com/article/10.1007/s11095-024-03757-4
②Quality and Safety Considerations for Therapeutic Products Based on Extracellular Vesicles

AMED

FY2025 ③Preparation of draft guideline for ensuring quality of therapeutic **native EV** products — **Step 1** ← We are here.

FY2026 Preparation of draft guideline for quality control of therapeutic **engineered EV** products — **Step 2**

These guidelines will be published from MHLW after the public consultation.

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Draft Guideline for Ensuring Quality of Therapeutic Native EV products Derived Human Cells (AMED, Representative is NIHS)

1. Introduction

2. Scope

3. Overview of EV product development

4. Quality control strategy for EV products
4.1 Overview of control strategy
4.2 Components of EV drug substance and drug product

5. Characterization of EV drug substance and drug product
5.1 Structure, composition, and physicochemical properties
5.2 Biological properties
5.3 Immunochemical properties
5.4 Impurities

6. Quality control of EV drug substance
6.1 Control of raw materials
6.1.1 Establishment and control of cell bank
6.1.2 Control of raw materials other than cell substrate
6.2 Manufacturing process control
6.2.1 Culture process
6.2.2 Purification process
6.3 Safety issues related to contaminants such as viruses
6.4 Process validation
6.5 Specifications
6.6 Reference materials
6.7 Stability testing

7. Quality control of EV drug product
7.1 Manufacturing process control
7.2 Additives
7.3 Specifications
7.4 Reference materials
7.5 Stability testing

8. Comparability assessment when manufacturing process is changed

Glossary

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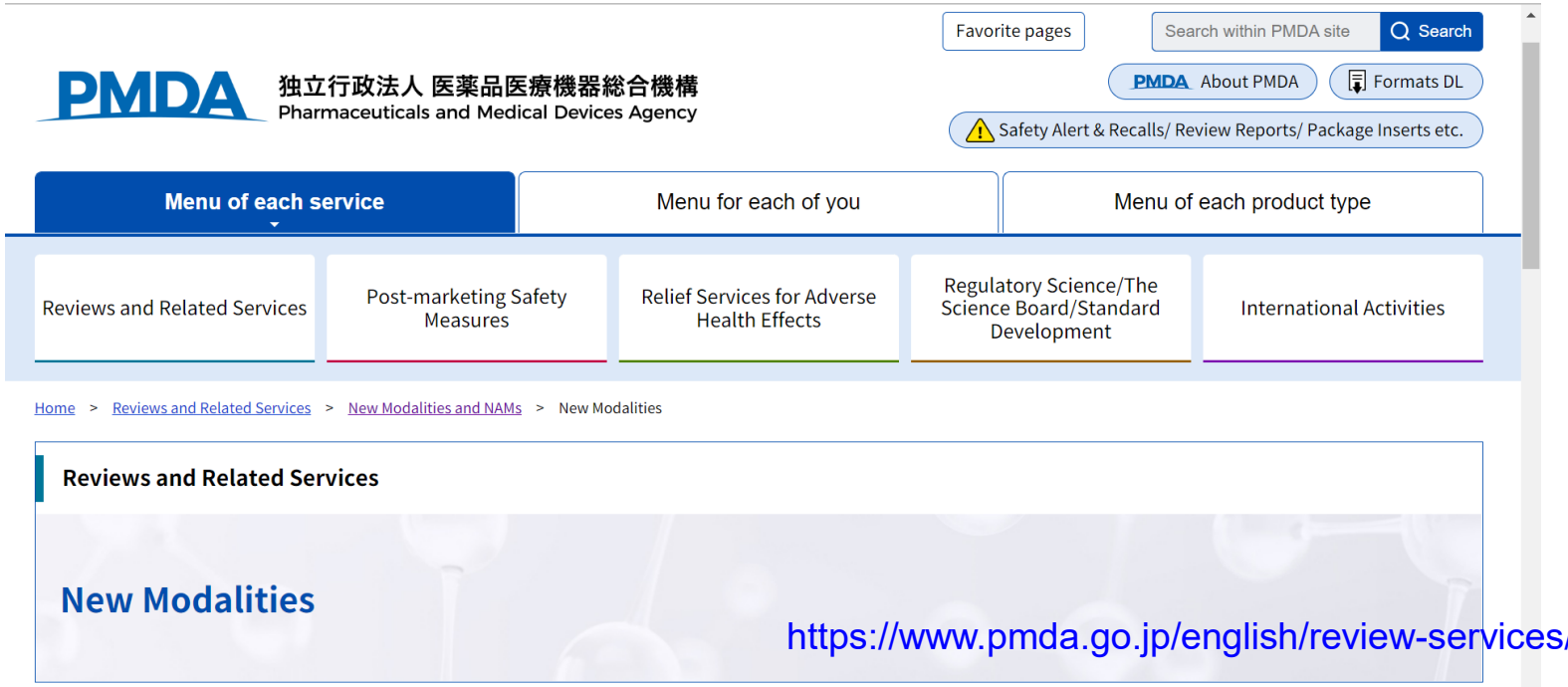
Establishment of Website for New Modalities

In recent years, the environmental surrounding drug discovery has undergone significant changes, and research and development utilizing technologies fundamentally different from those used in conventional drug development -so-called “new modalities”- has been accelerating. Research and development on new modalities are expected to provide new therapeutic options for various diseases that have been difficult to treat with traditional pharmaceuticals.

PMDA promotes the implementation of new modality pharmaceuticals and contributes to strengthening Japan’s drug discovery capabilities through initiatives such as consultations and support aimed at the practical application of innovate seeds of new modalities.



https://www.pmda.go.jp/english/review-services/0024.html

PMDA website (English version) has been updating!

◆Biosimilars

https://www.pmda.go.jp/english/review-services/reviews/0005.html

◆Regenerative medicine

https://www.pmda.go.jp/english/review-services/reviews/0003.html

◆GMO regulation (Cartagena Act)

https://www.pmda.go.jp/english/review-services/reviews/cartagena-act/0001.html

Conclusion

- PMDA efforts to accelerate the regulatory harmonization and convergence including the regulatory frameworks.

- PMDA efforts the scientific guideline to accelerate the developments of these new modalities.
  - ✓ Microbiome Medicines (LBP and FMT)
  - ✓ Extracellular Vesicles (EVs)
  - ✓ In vivo Gene Therapy Products
  - ✓ Phage Therapy Medicinal Products

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Thank you for your attention!

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